Ethical issues in establishing the efficacy and safety of long-acting injectable pre-exposure prophylaxis for HIV prevention: the HPTN 083 trial

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Two multinational clinical trials have shown safety and efficacy of long-acting injectable cabotegravir for HIV pre-exposure prophylaxis (PrEP). These results will alter the landscape of HIV prevention and related research. Nevertheless, designing and conducting this research involved several ethical issues. This Viewpoint describes how we managed ethical issues over the duration of one of these trials (HPTN 083). Specifically, we discuss the rationale for pursuing a long-acting injectable agent in the presence of effective oral PrEP, trial design choices, site selection and local standards of prevention, data monitoring and early stopping, effects of the COVID-19 pandemic, post-trial access, and assessment of long-term safety.

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Introduction

Two multinational clinical trials have shown safety and efficacy of long-acting injectable cabotegravir for HIV pre-exposure prophylaxis (PrEP).[1,2] Together, these results will alter the landscape of HIV prevention practices and research. As members of the protocol team in one of these trials, in this Viewpoint, we describe how we managed the ethical issues encountered during the design and conduct of the HIV Prevention Trials Network (HPTN) 083 trial.[1] This information provides additional context to understand the study results and offers lessons for future HIV prevention research.

HPTN 083 is a multicentre, randomised, double-blind, double-dummy, active-controlled, phase 2b/3 trial comparing the safety and efficacy of long-acting injectable cabotegravir given once every 8 weeks with daily oral tenofovir disoproxil fumarate and emtricitabine among cisgender men who have sex with men (MSM) and transgender women who have sex with men in Africa, Asia, South America, and the USA.[1] The study included 4566 randomly assigned participants in the intention-to-treat cohort and showed that long-acting injectable cabotegravir was superior to daily oral tenofovir disoproxil fumarate and emtricitabine for HIV prevention. The trial is ongoing in an open-label extension (NCT02720094).

HPTN 083 was done in accordance with the HPTN Ethics Guidance for Research,[3] which is based on conceptual and empirical ethics scholarship in the context of HIV prevention science. This guidance offers a practical approach to HIV prevention research that often takes place in the setting of normative guidances (such as the Declaration of Helsinki, UNAIDS and WHO guidance, and the Nuremberg code), that are not always consistent and might be conflicting; multiple policies and regulations; and in vulnerable populations across the world.[4]

The HPTN Ethics Guidance document includes 15 guidance points (GPs) that roughly follow the HIV prevention research lifecycle. The GPs relate to high-quality scientific and ethical research (GP1); research objectives and priorities (GP2); community engagement (GP3); local capacity and partnerships (GP4); study design (GP5); consent, assent, permission, and reconsent (GP6); addressing vulnerabilities (GP7); ethics review of research (GP8); standard of prevention (GP9); standards of care and treatment (GP10); independent data safety and monitoring (GP11); disseminating research results (GP12); sustaining capacity strengthening and infrastructure (GP13); continuing care for research participants (GP14); and post-trial access to effective interventions (GP15).

Here, we use the HPTN Ethics Guidance document as a framework for describing the ethics issues in HPTN 083. Specifically, we examine the rationale for pursuing a long-acting injectable agent in the presence of effective oral PrEP, trial design choices, site selection and local standards of prevention, data monitoring and early stopping, effects of the COVID-19 pandemic, post-trial access, and assessment of long-term safety. However, we do not review the range of well established practices that were important in ensuring the trial was ethically sound and met regulatory requirements. For instance, we do not describe all aspects of the GPs, such as standard ethical review (GP8) and consent (GP6). Similarly, active community engagement (GP3) was embedded in the trial from stages of early design to dissemination of results, which contributed to its successful implementation, but we do not discuss this point in detail here.

Trial rationale

As specified in GP2: "HIV prevention research should prioritize efforts that address public health needs, reduce health inequities, and are locally relevant."[3] Although the efficacy and safety of daily oral tenofovir disoproxil fumarate and emtricitabine PrEP is well established for cisgender MSM and has been shown to be effective in other groups, a clear need for expanding HIV prevention options exists, especially for those continuing to face disproportionate risk of HIV infection.[5] Drawing on lessons from contraceptive technology, having multiple preventive options would be desirable and would increase

the probability that one option would be acceptable to an individual at any given point in time.[6] Additionally, the efficacy of oral PrEP is largely contingent on adherence to taking pills and its associated challenges. Furthermore, use of oral PrEP might be difficult in some settings without incurring risks of stigma and intimate partner violence. If shown to be safe and effective, a long-acting agent might overcome some of these challenges. Moreover, in some settings, injections are viewed as more effective than oral medications.

The antiviral efficacy and safety profile of cabotegravir as part of HIV treatment regimens and its availability as a long-acting injectable agent made this drug well suited to be evaluated as a potential preventive intervention. After preventive efficacy was shown in a non-human primate model,[7,8] the safety, tolerability, and pharmacokinetics were assessed in two phase 2 studies of individuals not infected with HIV.[9–11]

Study design choices

Developing the appropriate study design for HPTN 083 involved complex scientific and ethical decision making, since it ultimately needed to meet the ethical obligation articulated in GP5 that "HIV prevention research should be designed to minimise risks and maximise benefits to study participants and their communities, while remaining scientifically sound."[3] The availability of an effective intervention ethically precluded the simple comparison of injectable cabotegravir with a placebo because participants assigned to placebo would be placed at unacceptable risk. Yet, a trial that compares active agents generally requires a larger sample size, which translates into challenges related to feasibility, cost, and time. Additionally, because an active-controlled trial does not directly compare the new medication against no intervention, estimates of absolute efficacy are complex and imprecise. With these concerns in mind, the team ultimately elected a randomised, active-controlled, double-dummy design—ie, participants were randomly assigned to receive either active injectable cabotegravir and placebo oral tenofovir disoproxil fumarate and emtricitabine or placebo injectable cabotegravir and active oral tenofovir disoproxil fumarate and emtricitabine. As such, this design allowed all participants to access an agent with known efficacy for treatment of HIV: one with proven preventive efficacy and one investigational. Although this design still involved risks because the preventive efficacy and safety of cabotegravir was not yet established in humans, the studies in non-human primates demonstrated preventive efficacy of cabotegravir and evidence from oral PrEP studies showed that antiretroviral agents can have preventive efficacy in humans. Thus, there was clinical equipoise regarding the two study groups. Nonetheless, although this design addressed important concerns related to participant safety, requiring participants to receive regular injections and a daily oral medication increased the burden and made the intervention substantially different from how it would be implemented if shown to be safe and effective. Those who might prefer an injectable approach to prevention might be disinclined to take a daily oral medication. However, including intensive counselling to teach about the need for adherence is possible in a short-term clinical trial, and would partly mitigate some of the potential challenges related to this design.

The use of a long-acting injectable agent also posed some challenges for research design. First were concerns related to the possibility that some participants might have adverse reactions to cabotegravir, which could be problematic if the participants were given a long-acting drug anticipated to remain in the body for at least 1 year after a single injection. To overcome this challenge, we implemented a short-acting oral cabotegravir lead-in of up to 5 weeks so that participants who were unable to tolerate cabotegravir would avoid long-term exposure.

Second were concerns related to the long half-life of injectable cabotegravir that would create a cabotegravir tail, with gradually waning drug concentrations following the last injection.[9–11] At some point, these concentrations would no longer have preventive efficacy, which could have been detrimental for participants who were still at risk of HIV but no longer receiving cabotegravir injections. The primary concern was the possibility that those who acquired HIV and had low concentrations of cabotegravir might be at risk of developing drug-resistant HIV making treatment more difficult. Consequently, the protocol contained a requirement to prevent this issue, known as covering the tail, with oral tenofovir disoproxil fumarate and emtricitabine for up to 1 year following the last injection, to prevent HIV infection in those at continued risk and prevent drug-resistant HIV infection.

Third, it was essential that the placebo injections looked as similar to the cabotegravir injections as possible. To maximise parity with the active injection, we selected a placebo of 20% intralipid solution that was visually indistinguishable from active cabotegravir and with similar viscosity. The intralipid formulation had a reportedly benign injection site reaction profile when used as a placebo in long-acting antipsychotic clinical trials.[12] Notably, in a previous study,[10] injection site reactions were a common adverse event among those receiving injectable cabotegravir. Therefore, maintaining the masking of participants in the HPTN 083 trial could have been challenging because of the anticipated high frequency of injection site reactions with active cabotegravir and low frequency of injection site reactions with placebo injections. However, despite the need for a realistic placebo injection to help maintain masking, using a placebo injection with a matching injection site reaction profile would have been ethically problematic because the risks of placebos must be minimised.

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Finally, statistical requirements posed challenges in terms of sample size with concomitant implications for the trial cost. Given the proven preventive effectiveness of daily oral tenofovir disoproxil fumarate and emtricitabine in MSM, a non-inferiority design was appropriate, requiring long-acting injectable cabotegravir to show not substantially lower efficacy than tenofovir disoproxil fumarate and emtricitabine, as opposed to requiring proof of superiority. A non-inferiority margin of 23% was calculated on the basis of results from previous placebo-controlled, randomised clinical trials, meaning that long-acting injectable cabotegravir could be 23% less effective than tenofovir disoproxil fumarate and emtricitabine and still be clinically beneficial.[13,14] Additionally, because long-acting injectable cabotegravir was presumed to offer an adherence advantage, if both active products had similar preventive activity, we hypothesised that injectable cabotegravir would have 25% greater efficacy than oral PrEP. Holding trial completion time constant, this assumption reduced the trial sample size from 25 645 to 4500 participants. This assumption was consistent with ethical considerations related to the anticipated social value of proposed research. In this case, social value could result from a new preventive intervention that might complement or have an advantage over standard interventions (eg, in terms of safety, effectiveness, ease of use, or acceptability). Explicitly incorporating the anticipated advantage into our trial design substantially reduced the sample size and associated resources required for the trial.

Site selection and local standards of prevention

Site selection involved identifying populations with known ongoing risk of HIV transmission, which was scientifically necessary to help ensure the research will be informative and ethically to meet a local priority. This selection included geographical locations with known high incidence (higher than 3 per 100 person-years) and young adults, MSM and transgender women who have sex with men, and individuals from racial and minority ethnic groups in the USA. We selected 43 sites in South Africa, the USA, Asia (Thailand and Vietnam), and South America (Argentina, Brazil, and Peru).

Additionally, to protect the wellbeing of participants, it was essential that sites were able to safely complete the trial. Making such a comprehensive assessment necessitated a review of local technical capacity (GP4) and local community engagement and support (GP3), to satisfy additional ethical requirements for research.

Further, local standards of prevention had to be appropriate. This requirement is captured in the HPTN GP9 regarding the standard of prevention: "HIV prevention researchers should partner with key stakeholders to provide a package of effective, comprehensive, and sustainable prevention services to all participants in HIV prevention research."[3] For the HPTN 083 trial, meeting this requirement included local reasonable access to oral PrEP. The ethical concern in this case was the possibility of undue inducement for participation in the trial if oral PrEP was unavailable.[15] In such circumstances, conceivably, some people might have enrolled in the trial because they wanted to receive oral PrEP, but would otherwise not be willing to participate because of numerous reasons such as time commitments, mistrust of the research process, or not wanting the experimental medication.

Data monitoring and early stopping

Monitoring the emerging safety and efficacy by a group of experts independent of the trial team and sponsors is an important mechanism to ensure research integrity and the wellbeing of research participants (GP11). During the first year of the trial, our team became concerned that injection site reactions were higher than expected and might indicate that inert placebo injections had a substantial rate of injection site reactions, prompting the team to request an ad hoc unblinded safety review. Following this review, the Data and Safety Monitoring Board recommended continuing the trial without any change. Notably, upon unblinding, the results showed that the intralipid placebo injections had a minimal and benign injection side-effect profile, fulfilling the initial design intent.

The original interim monitoring plan was to recommend early stopping of the blinded trial because of efficacy only if superiority was established, even though the aim was to show non-inferiority. This conservative approach was a safeguard against the possibility of low adherence in the tenofovir disoproxil fumarate and emtricitabine group and a strategy to gain more robust and conclusive evidence of efficacy shown by a superiority result. In the event of very low adherence, tenofovir disoproxil fumarate and emtricitabine might be a little better than placebo, and regulators (such as the US Food and Drug Administration) indicated that in such circumstances a tighter non-inferiority margin, or even superiority, would be needed to show that cabotegravir was significantly better than the placebo. However, if superiority over an already effective agent is shown, proof of efficacy is assured.

The COVID-19 pandemic, which developed during the blinded phase of the trial, understandably raised concerns about future participant safety and trial integrity due to potential trial disruptions, including, but not limited to, the ability or willingness of participants to attend study clinic visits to receive study medications as well as testing and monitoring. A specific concern related to determining efficacy was that the disruption to study clinic operations might prevent participants from accessing study medications. With medications unavailable, new infections could occur in both groups at a similar rate, which would dilute any differences between the randomised study groups and weaken scientific conclusions.

These concerns arose before the first planned interim analysis of the trial, scheduled to occur when 25% of the overall anticipated HIV infections were observed. Data to be presented at the May 20, 2020, Data and Safety Monitoring Board meeting were largely unaffected by the COVID-19 pandemic. However, before the meeting, the masked study team considered the potential future impact of the pandemic on study site activity restrictions and closures and the integrity of the trial. Based on these issues, the team determined that a change to the interim monitoring strategy was needed to a boundary based on the non-inferiority hypothesis. This modification would allow for early stopping with less extreme interim analysis results, potentially allowing the trial to end before being compromised by COVID-19-related disruptions. The masked HPTN Study Monitoring Committee (including the sponsor) and the independent Data and Safety Monitoring Board reviewed and endorsed this change before the meeting. The study team recognised that given the uncertainties, having a definitive answer to the primary endpoint would be preferable to potentially waiting longer for a stronger result that might be more convincing to multiple stakeholders. The new stopping rule was designed to be conservative at the first interim analysis, meaning that any evidence in favour of the experimental treatment would need to be extremely strong ($p<0·00006$) to stop the trial with only one quarter of the planned events (ie, HIV infections). The decision taken by the study team was fortuitous, and the study was stopped because the new monitoring stopping boundary was crossed. At the time of the Data and Safety Monitoring Board meeting, the interim analysis result did not cross the originally planned boundary for superiority, and the study might have continued. Nevertheless, due to the strong imbalance required for a decision to stop a trial at the first interim analysis, even on the basis of a non-inferiority hypothesis, there was clear statistical superiority for cabotegravir.

Effects of COVID-19

Akin to the majority of clinical research worldwide, HPTN 083 was affected by the COVID-19 pandemic. Most effects occurred after the blinded part of the study was stopped. Some of the ethical issues encountered are detailed elsewhere;[16] however, most notably, there was a marked variability in the impact of COVID-19 on different sites in the HPTN 083 trial. For example, some sites shut down completely, some were open but had fewer staff, others were open and fully operational but local regulations made transit complicated or unsafe, and some participants did not feel safe attending in-person study clinic visits. Site teams took several measures to maintain study integrity and help to ensure the wellbeing of participants and staff. To the extent possible, all sites maintained ongoing communication with study participants regardless of their ability to attend visits and provided support and resources for their health and safety. For instance, one site arranged for safe, private transportation to the study site. When sites closed, after careful vetting with local regulatory authorities and research ethics committees, teams engaged in extensive telephone or social media communication with participants.

Pharmaceutical companies involved with the trial also contributed to the response to the COVID-19 pandemic. Specifically, ViiV Healthcare (the manufacturer of cabotegravir) provided sites with additional resources (eg, masks, gloves, gowns, and cleaning supplies) for COVID-19-related use, which enhanced safety of participants and staff. In circumstances where there was limited ability to safely administer injectable cabotegravir, Gilead Sciences (the manufacturer of tenofovir disoproxil fumarate and emtricitabine) provided additional oral tenofovir disoproxil fumarate and emtricitabine for use during the pandemic. As outlined in a clarification memorandum provided to all sites, use of tenofovir disoproxil fumarate and emtricitabine for bridging purposes was permissible given the ethical obligation to provide an effective form of HIV prevention when injections could not be delivered safely.

Post-trial access

Consistent with most ethics guidelines,[3,17] the trial sponsors and ViiV Healthcare committed to supplying injectable cabotegravir to trial participants in the event of a superiority finding until it was locally available. This approach was acceptable to the team, participating sites, and ethics committees. However, the COVID-19 pandemic created supply chain issues when the blinded part of the trial was stopped earlier than expected, creating challenges related to cabotegravir supply and resulting in a delay in the transition of participants from the placebo cabotegravir and active tenofovir disoproxil fumarate and emtricitabine group to the active cabotegravir group if they chose to do so. Supply issues have since been resolved and an unblinded, open-label extension of the study, which is offering active cabotegravir to all participants, is currently ongoing.

Assessing long-term safety

Although the HPTN 083 trial showed that injectable cabotegravir was effective and safe in the short-term, early stopping of the trial precluded the collection of long-term safety data (the mean time on cabotegravir was 1·25 years instead of 3 years as originally planned). Consequently, the long-term safety of injectable cabotegravir for HIV prevention is being further explored in the extension of HPTN 083. Given the results of the blinded part of the study, information from this extension is crucial for meeting local needs and priorities (GP2). In this open-label extension study, some aspects of the delivery of cabotegravir have been simplified on the basis of lessons learnt in the blinded part of the study. For example, the oral lead-in for participants electing cabotegravir is optional. This decision was taken for several reasons. Most importantly, no severe reactions or side-effects

attributed to cabotegravir were observed in the oral lead-in or the injectable delivery phases that would be anticipated to have been caught during the oral phase. Further, the oral lead-in might be associated with a period of vulnerability for HIV acquisition because the time-to-onset of protection after initiating oral dosing is still not defined and relies on adherence to daily oral pill taking. This factor is especially relevant for those most likely to benefit from an injectable form of PrEP because they are vulnerable to lapses in oral pill taking that could lead to HIV infection in the setting of exposure if the oral lead-in is not completely adhered to.

Furthermore, the initial study results suggest that HIV acquisition during the cabotegravir tail might not result in the selection of resistance; although these data are reassuring, the small number of such events does not definitively preclude the possibility of tail-phase resistance.[18] Instead, the study team observed resistance in rare cases of PrEP failure in the cabotegravir group at high cabotegravir concentrations. The study team further observed delays in detection of HIV infection using conventional HIV testing algorithms, which occurs with daily oral PrEP with tenofovir disoproxil fumarate and emtricitabine, but was even more pronounced and lengthened with cabotegravir. As such, the open-label extension of HPTN 083 will evaluate the potential benefits of an expanded and more sensitive algorithm to detect incident infection. Whether HIV resistance can be avoided with more rapid incident detection is an ongoing research question that the open-label extension will attempt to answer. Meanwhile, transparently discussing these complexities and uncertainties with participants and other stakeholders is essential.

Conclusion

We navigated an array of ethical issues in the HPTN 083 trial in accordance with the HPTN Ethics Guidance. Some novel strategies that were done to protect participants and study integrity during unforeseen and unprecedented disruptions, such as deliberating about the appropriateness of stopping boundaries given exigent circumstances, might be useful in future trials. However, this strategy necessitates having access to those with specific expertise to ensure ethical and scientific appropriateness and to be able to accurately communicate this to key stakeholders. Other strategies, such as using a double-dummy design to balance participants' welfare while being able to answer an important research question, might no longer be feasible in HIV prevention science because of the required size and cost of such trials; however, alternative regulatory pathways for product approvals have yet to be defined and successfully implemented. Nevertheless, descriptions of how research teams manage ethical issues in research should be encouraged to facilitate future ethical research and deliberations.

Contributors

JS, DJD, and RJL conceptualised the manuscript. JS and DJD created the initial draft. All authors reviewed, edited, and approved the final version of the manuscript.

Declaration of interests

JS is a member of the Merck KGaA Bioethics Advisory Panel and Stem Cell Research Oversight Committee, IQVIA Ethics Advisory Panel, Aspen Neurosciences Scientific Advisory Board, and a Merck Data Monitoring Committee; is a consultant for Biogen; and has consulted for Portola Pharmaceuticals. BG is a member of scientific advisory boards for Merck, GSK, VIR, and Janssen; and has received honoraria for scientific presentations from GSK and Merck, outside the submitted work. RJL is a member of scientific advisory boards for Merck and Gilead; and has received honoraria for scientific symposium presentations from Roche and Janssen, outside the submitted work. All other authors declare no competing interests.

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